[Document] Claims

[Claim 1]

A method for making a two phase solution of which the phase state changes through temperature conversion react, characterized by comprising the reaction step of stirring a material solution of which the reaction solvent is a solution of which the phase state changes in a reversible manner between a two phase solution state and a uniform solution state when the temperature fluctuates over or below a certain constant temperature within a reaction container at a predetermined temperature so that a uniform solution is gained and reacts; and the cooling step of cooling the uniform solution without cooling the reaction container so that a two-phase solution is gained within the reaction container.

[Claim 2]

The method for making a two phase solution of which the phase state changes through temperature conversion react according to Claim 1, characterized in that, in said cooling step, a portion or the entirety of the uniform solution is extracted from a reaction container, the extracted uniform solution is cooled by a cooler and the two-phase solution that has been gained through cooling is put back into the reaction container.

[Claim 3]

The method for making a two phase solution of which the phase state changes through temperature conversion react according to Claim 1, characterized in that said cooling step is the step of putting a solid of which the temperature is lower than that of the reaction container into the uniform solution within the reaction container so that the uniform solution is cooled.

[Claim 4]

The method for making a two phase solution of which the phase state changes through temperature conversion react according to Claim 1, characterized in that said cooling step is the step of mixing a compound having a low boiling point directly into the uniform solution within the reaction container so that the uniform solution is cooled.

[Claim 5]

The method for making a two phase solution of which the phase

state changes through temperature conversion react according to any of Claims 1 to 4, characterized by further comprising the product solution gaining step of extracting the product solution phase from the two-phase solution that has been gained within the reaction container after said cooling step.

[Claim 6]

The method for making a two phase solution of which the phase state changes through temperature conversion react according to Claim 5, characterized in that the solvent phase that remains after the extraction of said product solution phase is reused in the next reaction.

[Claim 7]

The method for making a two phase solution of which the phase state changes through temperature conversion react according to any of Claims 1 to 6, characterized in that, in the two-phase solution stage of said reaction solvent, one phase is made of a cycloalkane compound and the other phase is made of one or more types selected from among nitroalkane, nitrile, alcohol, alkyl halide, carbonate, imidazolidinone, carbodiimide, ester, carboxylic acid, aldehyde, ketone, ether, urea, amide compounds and sulfoxide.

[Claim 8]

An apparatus for making a two phase solution of which the phase state changes through temperature conversion react, characterized by comprising: a reaction container having a heating means for heating the reaction container attached; a stimulating means for physically stimulating a material solution within the reaction container so as to gain a uniform solution; and a cooling means for cooling the uniform solution within the reaction container without cooling the reaction container.

[Claim 9]

The apparatus for making a two phase solution of which the phase state changes through temperature conversion react according to claim 8, characterized in that said cooling means is a means for extracting the uniform solution from a reaction container, cooling the extracted uniform solution with a cooler and returning the two phase solution that has been gained through cooling into the reaction container, a means for putting a solid of which the temperature is lower than that of the

reaction container into the uniform solution within the reaction container, or a mixing means for mixing a compound having a low boiling point directly into the uniform solution within the reaction container.

[Document] Specification

[Name of the Invention]

Method for Making Two-Phase Solution of which Phase State Changes as a Result of Temperature Conversion React, and Apparatus for Implementing This

[Field of the Invention]

[0001]

The present invention relates to a method for making a two-phase solution of which the phase state changes as a result of temperature conversion react, of which the operability and reproducibility are excellent, as well as to an apparatus for implementing this.

[Background Technology]

[0002]

In a chemical process, in the case where a sequential mixture and separation operation can be carried out with ease, sequential work efficiency can be dramatically increased. Presently, it is known that change in temperature causes phase solving/phase separation in a solvent mixture that is formed of a combination of a solvent having a perfluoroalkyl group, and a general organic solvent (I. T. Horvath, J. Rabai, Science, 1994, 266, 72; J. A. Gladysz, Science, 1994, 266, 55).

Japanese Unexamined Patent Publication H15 (2003)-62448 shows a combination of a cycloalkane and a polar solvent as an example of a solvent mixture where phase solving/phase separation is caused.

[0003]

Fig 1 is a conceptual diagram illustrating the theory that solvent mixture causes phase solving/phase separation. (A) in Fig 1 shows a state where single organic solvents or mixed organic solvents are separated. For example, a solvent that dissolves a reactive material is used as one solvent, and a solvent that dissolves a catalyst or a reaction adjuvant is used as the other solvent. (B) is a step where reaction progresses under such temperature conditions that the solvent is in a state where a uniform phase solving mixture solvent system. (C) shows the state of a separated solvent system where solvent phases of which the main components are solvents that form reversible solvent systems under the above described temperature conditions are separated into phases in which products are dissolved and catalysts or a reaction

adjuvant are dissolved. Then, the phase in which the products are dissolved (product solution) is separated and taken out so as to be used for a desired application, while the phase in which reaction adjuvant dissolves (catalyst or reaction adjuvant solution) is recycled (D).

[0004]

Since the compatibility polyphase organic solvent which contains the cycloalkane of a description in Japanese Unexamined Patent Publication H15 (2003)-62448 can be made to repeat by slightly changing the temperature, can be applied to a wide range of chemical processes etc.

(Non-Patent Document 1) I. T. Horvath, J. Rabai, Science, 1994, 266, 72; J. A. Gladysz, Science, 1994, 266, 55

(Patent Document 1) Japanese Unexamined Patent Publication H15 (2003)-62448 (Claim 1)

[Description of the Invention]

[Problem to be solved by the invention]

[0005]

However, in the case where a multi-stage successive reaction process is carried out by repeating successive phase solving/phase separation, the temperature of the reaction containers should be increased or lowered at each stage, and thereby, the temperature of the solution changes, so that the phase structure of the solution changes. This causes a problem, such that control becomes difficult, particularly on a plant scale, where the capacity is large. In addition, when the temperature of the reaction containers on a plant scale is increased or lowered at each stage, a problem arises, such that the amount of use of utilities, such as electrical power and cooling water, becomes massive, increasing the cost for manufacture.

[0006]

Accordingly, an object of the present invention is to provide a method for making a two-phase solution of which the phase state changes due to temperature conversion which is excellent in operativity and efficiency in production, as well as an apparatus for implementing this.

[Disclosure of the Invention]

[0007]

Under these circumstances, the present inventors conducted diligent research, and as a result, discovered that phase separation

automatically occurs when the temperature is lowered, while phase solving does not occur even when the temperature is increased, unless provided with certain physical stimulation, in a solvent mixture where phase solving and phase separation are repeated in a reversible manner, by changing the temperature; accordingly, the two-phase solution is maintained even when the uniform solution within the container is cooled without cooling the container that has been heated in order to make reaction occur, so that the two-phase solution is gained, and after that, the two-phase solution is kept within the container in this heated condition; accordingly, a multi-stage successive reaction process can be carried out while maintaining the temperature of the reaction container, even after the product solution has been removed from the two-phase solution, and as a result, excellent operativity and efficiency in production can be gained, and thus, the present invention was completed.

[0008]

That is to say, the present invention provides a method for making a two-phase solution of which the phase state changes as a result of temperature conversion react, characterized by having: a reaction step, where a material solution of which the reaction solvent is a solution of which the phase state changes in a reversible manner between a two-phase solution state and a uniform solution state when the temperature fluctuates over or under a certain constant temperature is stirred at a predetermined temperature within a reaction container, so that a uniform solution is gained and reaction occurs; and a cooling step, where the uniform solution is cooled without cooling the reaction container, so that a two-phase solution is gained within the reaction container.

[0009]

In addition, the present invention provides an apparatus for making a two-phase solution of which the phase state changes as a result of temperature conversion react, characterized by having: a heating means for heating a reaction container; a reaction container with a stimulation means for providing physical stimulation to a material solution within the reaction container so that a uniform solution is gained attached thereto; and a cooling means for cooling a uniform

solution within the reaction container without cooling the reaction container.

[Effect of the Invention]

[0010]

According to the method for making a two-phase solution of which the phase state changes as a result of temperature conversion react of the invention, cooling and reheating of one reaction container become unnecessary, and the temperature can be maintained constant, and therefore, efficiency in production greatly increases. In addition, after the completion of reaction in one process, the temperature of the reaction solution where the next reaction is to occur in the process becomes quickly constant (heated condition), and therefore, the period of time for the changing of the temperature can be greatly shortened in a multi-stage successive process or the like.

[Best Mode for Carrying Out the Invention]

[0011]

In a method for making a two-phase solution of which the phase state changes as a result of temperature conversion react according to the present invention, the reaction step is a step for making a material solution react by stirring the material solution within a reaction container at a predetermined temperature and thus gaining a uniform solution. The reaction solvent of the material solution is a solution where the state of phase, that is, the state of a two-phase solution and the state of a uniform solution, is changed in a reversible manner when the temperature fluctuates over and under a certain constant temperature (hereinafter also referred to as "solvent mixture"). Though this solvent mixture is not particularly limited, a solvent mixture of an organic solvent having a low polarity and an organic solvent having a high polarity can be cited as an example.

[0012]

As for the organic solvent having a low polarity, alkane, cycloalkane, alkene, alkyne, aromatic compounds and the like can be cited as examples. From among these, cycloalkane compounds are preferable. As the cycloalkane compound, cyclohexane, methyl cyclohexane, decalin and the like can be cited as examples, and from among these, cyclohexane has a relatively high melting point of 6.5 °C, and thus, is preferable

in that the product of reaction, for example, can be solidified and separated.

[0013]

As for the organic solvent having a high polarity, nitroalkane, nitrile, alcohol, alkyl halide, carbonate, imidazolidinone, carbodiimide, ester, carboxylic acid, aldehyde, ketone, ether, urea, amide compounds and sulfoxide can be cited as examples, and one type can be used alone, or two or more types can be combined for use.

[0014]

The material solution that is used in the present invention contains a variety of substances which relate to the reaction, such as a solute, a catalyst, a ground substance and a reaction adjuvant, in addition to the solvent mixture. As concrete examples of the material solution, a mixed solution of cyclohexane, dimethyl formamide, octadecyl amine and benzoyl chloride, a mixed solution of cyclohexane, dimethyl formamide, octadecyl amine and acetic acid anhydride, a mixed solution of cyclohexane, N, N'-dimethyl imidazolidinone, octadecyl alcohol and benzoic acid, and a mixed solution of decalin, N, N'-dimethyl imidazolidinone, hexadecanethiol and methyl acrylate can be cited. In the above description, octadecyl amine, octadecyl alcohol and hexadecanethiol dissolve in cyclohexane or decalin, and the above described benzoyl chloride, acetic acid anhydride and methyl acrylate dissolve in dimethyl formamide, N, N'-dimethyl imidazolidinone, and the like.

[0015]

The method for setting the material solution at a predetermined temperature within the reaction container is not particularly limited, and a method for introducing a material solution that has been heated to a predetermined temperature in advance into a reaction container, a method for introducing a material solution at room temperature into a reaction container, and after that, maintaining the material solution at a predetermined temperature by turning on the heater for heating the reaction heater, and a method for setting a reaction container to a temperature which exceeds a predetermined temperature by turning on the heater for heating the reaction container and introducing the material solution at room temperature into this reaction container so that the

material solution is maintained at the predetermined temperature can be cited as examples. From among these, the method using the heater for heating the reaction container is preferable in that a separate container for heating the material solution is not required. The predetermined temperature is a reaction temperature that is appropriately determined on the basis of the type of material solution and reaction. In the reaction step, the method for stirring the sample that has been heated to a predetermined temperature is not particularly limited, and a mechanical stirring method for stirring with a stirring rod with stirring blades on the end portion, a bubbling method for introducing bubbles by blowing a nitrogen gas into a sample, and a vibration stirring method for making a sample container or a sample vibrate can be cited as examples. From among these, the mechanical stirring method for stirring with a stirring rod with stirring blades on the end portion or the bubbling method for introducing bubbles by blowing a nitrogen gas into a sample are preferable, in that the required apparatus is simple and the efficiency in stirring is high. The solvent mixture that is used in the present invention does not become a uniform solution simply by being heated to a predetermined temperature, but rather, the phases dissolve each other by providing constant physical stimulation. Accordingly, appropriate stirring conditions for the reaction step are selected as conditions for gaining a uniform solution. After a uniform solution has been gained, it may be maintained for a predetermined period of time at the predetermined temperature. The predetermined period of time is the time for reaction, and an appropriate period is determined on the basis of the type of the solvent used, the reaction and the purpose of the reaction. Phase separation naturally occurs in the solvent mixture that is used in the present invention when the temperature lowers, and therefore, a uniform solution is maintained at a temperature that is no lower than the temperature at which phase separation occurs during the predetermined period of time.

[0016]

The cooling step is a step for gaining a two-phase solution within the reaction container by cooling the uniform solution without cooling the reaction container. As the method for cooling the uniform solution without cooling the reaction container, though there is no

special limitation, a method for extracting a portion or the entirety of the uniform solution from the reaction container, cooling the extracted uniform solution with a cooler, and returning the two-phase solution gained through this cooling to the reaction container, a method for putting a solid of which the temperature is lower than that of the reaction container in the uniform solution within the reaction container, and a method for directly mixing a compound having a low boiling point into the uniform solution within the reaction container can be cited. "Without cooling the reaction container" means the opposite of cooling the sample within the reaction container by cooling the reaction container, and includes cooling of the reaction container when the sample within the reaction container is cooled.

[0017]

According to the method for extracting a portion or the entirety of the uniform solution from the reaction container, cooling the extracted uniform solution with a cooler, and returning the two-phase solution gained through this cooling to the reaction container, as the apparatus that is used in this method, a sampler with a cooling apparatus, for example, can be used in the case where the apparatus is a small-scale reaction apparatus. This sampler has the same mechanism as a syringe, and as the cooling apparatus, an apparatus where water is made to flow through a jacket that is formed around the cylinder of the sampler, for example, can be used. In addition, in the case of a large-scale reaction apparatus, an external cooling unit apparatus which is formed of an external cooler, a pump and pipes for linking these to form a circulation system can be used.

[0018]

In addition, in accordance with the method for putting a solid of which the temperature is lower than that of the reaction container in the uniform solution within the reaction container, as the apparatus that is used in the method, a glass rod or a metal rod with a cooling apparatus can be cited as an example. In addition, as the compound having a low boiling point that is mixed into the uniform solution within the reaction container, n-heptane, of which the boiling point is 25 °C, can be cited as an example. When a low boiling point compound makes direct contact with the uniform solution within the reaction container, it

absorbs evaporation heat from the solution, thus cooling the solution. The evaporated compound having a low boiling point is liquefied by a gas vaporizer, and is put back in the reaction container. The uniform solution can be cooled by repeating this procedure. The uniform solution that has been cooled in accordance with the above described method automatically separates into two phases when the temperature is no higher than a predetermined temperature. In the two-phase solution that is gained in the cooling step, one phase is made of a product solution where a product of reaction has been dissolved in an organic solvent having a low polarity, such as cyclohexane, and the other phase is made of a solution where a catalyst or a reaction adjuvant has been dissolved in an organic solvent having a high polarity, such as dimethyl formamide.

[0019]

In the cooling step, a two-phase solution is gained within the reaction container after cooling. In the case where the cooling method is a method using a solid of a low temperature or a method using a compound having a low boiling point, phases are separated within the reaction container, and therefore, no specific operation is required, and the solution can be left as it is. Meanwhile, in the case of the method for extracting a portion or the entirety of the uniform solution from the reaction container and cooling the extracted uniform solution with a cooler, the two-phase solution that was gained through cooling is returned to the inside of the reaction container. As the cooling method in the cooling step, the method for extracting a portion or the entirety of the uniform solution from the reaction container and cooling the extracted uniform solution with a cooler is preferable. That is to say, in the case of cooling within the reaction container using a solid of a low temperature or a compound having a low boiling point, the reaction container being heated is also cooled, making the efficiency in cooling poor. Furthermore, since the reaction container cools down, it becomes necessary to heat the remaining solvent at the time of reuse after the product solution is extracted, and thus, the cost of the reaction increases. In contrast, according to the method for cooling with an external cooling apparatus or cooler, it is possible to cool only the reaction solution, thus making the efficiency in cooling high. In addition, even when the solution that has been separated into two phases

is heated after being put back into the reaction container being heated, there is no physical stimulation, and therefore, the state where the solution is separated into two phases can be maintained.

[0020]

After the cooling step, the phase of the product solution is extracted from the two-phase solution that was gained within the reaction container, and is used for the intended application as it is, or after the solvent has been removed, if necessary. In addition, in the case where a multi-stage consecutive reaction process is carried out, it is preferable to leave the solvent phase that has been left after the extraction of the phase of the product solution to be left as it is within the reaction container being heated, in order to minimize the thermal energy for heating the reaction container again at the time of reuse of the remaining solvent phase, and thus suppress the cost for reaction.

[0021]

In addition, the reaction apparatus used for the two-phase solution of which the phase state changes when as a result of temperature conversion according to the present invention is provided with a heating means for heating a reaction container, a reaction container with a stimulating means for physically stimulating a material solution within the reaction container so as to gain a uniform solution, and a cooling means for cooling the uniform solution within the reaction container without cooling the reaction container.

[0022]

As for the heating means for heating the reaction container, though there are no particular limitations, an embedded heater that is provided within a wall of the reaction container can be cited as an example. This heater is connected to a temperature control mechanism for usually controlling the temperature within the reaction container.

[0023]

As for the stimulating means for physically stimulating the material solution within the reaction container so as to gain a uniform solution, a stirring rod with stirring blades on the end portion, a bubbling apparatus with a bubble introducing pipe for introducing bubbles into the material solution and a bubble generator, and a vibrator for making the reaction container or the material solution vibrate can

be cited as examples.

[0024]

As for the cooling means for cooling the uniform solution within the reaction container without cooling the above described reaction container, a means for extracting the uniform solution from the reaction container, cooling the extracted uniform solution with a cooler, and returning the two-phase solution that was gained through cooling into the reaction container, a means for putting a solid of which the temperature is lower than the temperature of the reaction container in the uniform solution within the reaction container, and a mixing means for mixing a compound having a low boiling point directly into the uniform solution within the reaction container can be cited.

[0025]

Next, the invention is described further concretely by citing an example, but this is merely illustrative, and does not limit the present invention.

(Example 1)

[0026]

A tabletop apparatus having a built-in block heater having cylindrical glass receptacles having a diameter of 20 mm and a height of 60 mm as reaction containers was used, and chemical reactions were made to occur through processes under the following reaction conditions. 2 ml of cyclohexane in which octadecyl amine (51 milligrams) was dissolved, and 2 ml of dimethyl formamide (DMF) in which benzoyl chloride (49 milligrams) was dissolved were put into a reaction container of which the temperature was 25 °C so as to prepare a material solution. At this time, the liquid separated into two phases.

[0027]

Next, the reaction container was heated so that the temperature became 60 °C, and at the point where temperature of the solution reached 48 °C, a nitrogen gas was blown directly into the solution and physical stirring was carried out, so that the solution immediately became a uniform solution. Next, a cooler in syringe form with a cooling apparatus was used, and 3.6 ml of the uniform solution was drawn into the cooling container from the main process container and left undisturbed, and then, the solution separated into two phases when the

temperature fell to approximately 40 °C. After the solution was left for an additional two minutes, the liquid was gradually returned from the cooler to the main process reaction container that was heated to 60 °C. Though this solution returned to no lower than 48 °C when left as it is, no strong physical stirring, such as blowing in of a nitrogen gas, was carried out, and the state of two phases was maintained.

[0028]

The product solution portion which was the upper phase in the two-phase solution within the reaction container in the heated state of 60 °C was extracted, and the solvent was removed, and it was confirmed that the product of reaction was N-octadecylbenzamide (yield: 96%). In addition, the solution that remained within the reaction container was a dimethyl formamide solution which was heated to no lower than 48 °C and in which benzoyl chloride was dissolved, and was in such a state as to be reusable as a portion of a material solution for the reaction in the next stage.

(Example 2)

[0029]

A tabletop apparatus having a built-in block heater having cylindrical glass receptacles having a diameter of 20 mm and a height of 60 mm as reaction containers was used, and chemical reactions were made to occur through processes under the following conditions for reaction. 2 ml of cyclohexane in which 2-amino butyric acid 3, 4, 5-tris octadecyloxy benzyl ester (60 milligrams) was dissolved, and 2 ml of dimethyl formamide (DMF) in which 9-fluorenyl methoxy carbonyl amino acetic acid (57 milligrams), diisopropyl carbodiimide (25 milligrams) and 1-hydroxy benzotriazole (55 milligrams) were dissolved, and which was stirred for 90 minutes, were put in a reaction container of which the temperature was 25 °C, so that a material solution was prepared. At this time, the liquid separated into two phases.

[0030]

Next, the reaction container was heated so that the temperature became 60 °C, physical stirring was carried out with a stirring rod with stirring blades at the end at the point where the temperature of the solution reached 48 °C, and then, the solution immediately became a uniform solution. Next, a glass rod having a diameter of 8 mm with a

cooling apparatus which was cooled to 5 °C was put in the main process solution so as to lower the temperature of the solution, and thereby, the solution separated into two phases. After the solution separated into two phases, the glass rod with the cooling apparatus was pulled out, and the solution was left as it is. The temperature of the solution increased afterwards, and even when the temperature became no less than 48 °C, the state where the solution was separated into two phases was maintained.

[0031]

When the product solution portion which was the upper phase in the two-phase solution within the reaction container in a heated state of 60 ° C was extracted, and the solvent was removed, 2-[2-(9H-fluoro-9-ylmethoxy carbonyl-amino)-acetyl amino]-3-methyl-butyric acid 3, 4, 5-tris octadecyloxy benzyl ester, which was the target product of reaction, was gained with a yield of 95 %.

(Example 3)

[0032]

A tabletop apparatus having a built-in block heater having cylindrical glass receptacles having a diameter of 20 mm and a height of 60 mm as reaction containers was used, and chemical reactions were made to occur through processes under the following conditions for reaction. 2 ml of cyclohexane in which octadecyl amine (51 mg) was dissolved, and 2 ml of dimethyl imidazolidinone (DMI) in which acetic acid anhydride (20 mg) was dissolved was put into a reaction container of which the temperature was 25 °C, so that a material solution was prepared. At this time, the liquid separated into two phases.

[0033]

Next, the reaction container was heated so that the temperature became 60 °C, and at the point where the temperature of the solution reached 48 °C, a nitrogen gas was blown directly into the solution, and physical stirring was carried out, and then, the solution immediately became a uniform solution. Next, n-pentane of which the temperature was 25 °C was gradually poured into this uniform solution. The N-pentane immediately started vaporizing, and at the point where the solution separated into two phases, the n-pentane stopped being poured. The

n-pentane almost completely vaporized when left for approximately 10 minutes, and even when the temperature of the solution became no lower than 48 °C, the state where the solution was separated into two phases was maintained.

[0034]

When the product solution portion which was the upper phase in the two-phase solution within the reaction container in a heated state of 60 °C was extracted, and the solvent was removed, N-octadecyl acetamide was gained (yield: 97%).

[Industrial Applicability]

[0035]

A method for making a two-phase solution of which the phase state changes as a result of temperature conversion react and an apparatus that is used for this according to the second invention can be applied to tabletop chemical process apparatuses for testing and research, flow system chemical reaction apparatuses and large-scale reaction plants.

[Brief Description of the Drawings]

[0036]

[Fig 1]

Fig 1 is a schematic diagram illustrating the thesis that a solvent mixture causes phase solving/phase separation.

[Document] Abstract

[Abstract]

[Problem to be Solved]

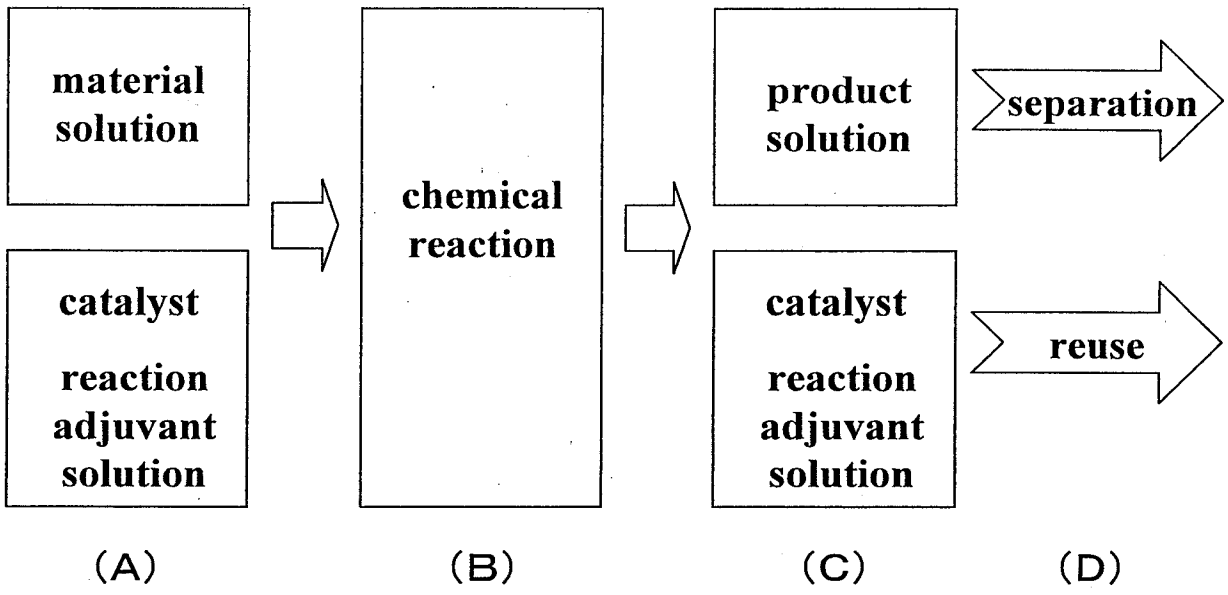
To provide a method for making a two-phase solution of which the phase state changes due to temperature conversion which is excellent in operativity and efficiency in production, as well as an apparatus for implementing this.

[Solution]

A method for making a two phase solution of which the phase state changes through temperature conversion react, characterized by comprising the reaction step of stirring a material solution of which the reaction solvent is a solution of which the phase state changes in a reversible manner between a two phase solution state and a uniform solution state when the temperature fluctuates over or below a certain constant temperature within a reaction container at a predetermined temperature so that a uniform solution is gained and reacts; and the cooling step of cooling the uniform solution without cooling the reaction container so that a two-phase solution is gained within the reaction container.

[Selected figure] none

Fig 1


material solution
catalyst
reaction adjuvant solution
chemical reaction
product solution
catalyst
reaction adjuvant solution
separation
reuse
(A)
(B)
(C)
(D)